Do patients with obstructive sleep apnoea deserve new dedicated antihypertensive strategies?

Renaud Tamisier,[1,2] Patrick Lévy,[1,2] Jean-Louis Pépin[1,2]

Hypertension affects 25% of the adult population and remains a leading cause of cardiovascular mortality, accounting for 13.5% of all deaths. Half of all strokes and ischaemic heart disease events are attributed to hypertension.[1 2] Most patients exhibit grade I hypertension (systolic blood pressure of 140–159 mm Hg and/or diastolic blood pressure of 90–99 mm Hg) without coexisting cardiovascular disease. Effective reduction of blood pressure in this population significantly reduces stroke and death.[3]

Obstructive sleep apnoea (OSA) is now recognised as a risk factor for the development of hypertension in European and the US International Guidelines. In OSA, elevation of blood pressure is in part due to intermittent hypoxaemia leading to increased sympathetic tone and impaired baroreflex gain.[4] Altered arterial vasoconstriction and vasodilatation[5] owing to stimulation of the renin-angiotensin-aldosterone system (RAAS)[6] are also significant contributors. Although OSA and hypertension are tightly linked in a dose-response manner, the impact of short-term OSA treatment on blood pressure reduction in unselected patient populations with OSA is rather mild, about 2 mm Hg reduction in 24-hour mean blood pressure. This effect is slightly greater in patients who are compliant with CPAP or mandibular advancement devices, presumably by allowing rapid eye movement (REM) sleep at the end of the night to be free of obstructive respiratory events.[7–9]

It stands to reason that treatment strategies combining OSA treatment and pharmacological antihypertensives would be synergistic.[10 11] Previous studies[10 11] have demonstrated that in hypertensive patients with OSA, losartan or valsartan are by far more effective than CPAP in reducing blood pressure, even if nocturnal blood pressure is better controlled when CPAP is used concurrently with these medications. This underlines the need for specific strategies to be further studied in hypertensive patients with OSA, as a distinct response is expected compared with the general non-OSA hypertensive population.

The study presented in this issue of *Thorax* by Serinel *et al*[12] attempted to address one piece of the puzzle regarding a better strategy for managing OSA-related hypertension. Using a well-established cross-over randomised controlled trial design, the authors explored whether chronotherapy would be of particular benefit in hypertensive patients with OSA. As hypertension in OSA is classically nocturnal and aggravates during REM sleep, the authors hypothesised that the decrease in nocturnal blood pressure would be superior by administrating perindopril in the evening compared with in the morning. Chronotherapy in essential hypertension[13] or in hypertensive diabetics[14] improves the blood pressure-lowering effect of pharmacotherapy during the night without weakening its daytime effect. The goal of administering antihypertensives in the evening is to restore the normal circadian dipping profile of blood pressure, which is the decrease of > 10% in sleep-time compared with daytime blood pressure during wakefulness. In the present study, however, an evening administration of perindopril did not lead to a superior effect on blood pressure control compared with morning administration in hypertensive patients with untreated moderate-to-severe OSA. In fact, daytime systolic blood pressure was more effectively reduced with morning than with evening administration of perindopril. These results highlight the complexities and differences when treating hypertension in patients with OSA. Chronotherapy alone is not adequate to improve nocturnal hypertension and it actually leads to poorer blood pressure control during daytime in this patient population. In the last part of the study, both groups were using CPAP for 8 weeks in an open-label design. This combined treatment (ie, ACE inhibitors and CPAP) further reduced the systolic blood pressure by an additional 3 mm Hg during sleep, which confirms the findings of previous reports.[10 11]

The study by Serinel *et al*[12] is a well-conducted and analysed RCT. Some limitations may be the absence of a non-OSA hypertensive group and not using sham-CPAP, although these might have had only a marginal impact on the reported results. Moreover, it remains unclear if the negative results of chronotherapy with ACE inhibitors is a class-effect or applicable to all antihypertensives. Ultimately, a major limitation in the field of sleep apnoea and hypertension, which is not unique to the study by Serinel *et al*, is the relatively small sample sizes and the short-duration of follow-up (n=79 and follow-up of 6 weeks in the study by Serinel *et al*). This is far less than the 3013 patients included in the MAPEC study who were followed for a median of 5.6 years. The MAPEC investigators found a significant reduction in cardiovascular risk using evening administration of antihypertensives.[15] The OSA community must convince academic and industrial funders of the rationale for defining specific indications for medications in OSA-related hypertension.

A major concept arising from the study by Serinel *et al*, and previous ones in this field is that OSA-related hypertension is a true 'resistant hypertension' that requires dedicated studies and specific guidelines. For example, a non-dipping profile is typical in these patients and such a profile, even in isolation, is related to a higher risk of cardiovascular disease and death.[16] In the MAPEC study, chronotherapy improved nocturnal blood pressure and led to a 17% reduction in cardiovascular risk for each 5 mm Hg reduction in systolic blood pressure during sleep ($p<0.001$) in patients with essential hypertension.[15] The negative findings by Serinel *et al*[12] demonstrate that such results cannot be extrapolated to the OSA population. While CPAP is the gold standard treatment for OSA, it is not necessarily effective in reducing blood pressure, particularly if adherence to treatment is low. In the Sleep Apnea CardioVascular Endpoints (SAVE) study, there was no difference in cardiovascular outcomes in patients with OSA and established coronary or cerebrovascular disease with a mean duration of CPAP treatment of 3.7 years, compared with usual care. Moreover, mean CPAP adherence of 3.3 hours per night did not lead to any improvement in office arterial blood pressure.[17] Taken together, these results emphasise the need to rethink therapeutic approaches in order to effectively reduce the blood pressure in different subpopulations of patients with OSA. Intrinsic and extrinsic factors that

[1]HP2 Laboratory, Inserm, Univ. Grenoble Alpes, Grenoble, France; [2]Pôle Thorax et Vaisseaux, Grenoble Alpes University Hospital, Grenoble, France

Correspondence to Dr Renaud Tamisier, Laboratoire EFCR, CHU de Grenoble, CS 10217, 38043 Grenoble cedex 09, France; rtamisier@chu-grenoble.fr

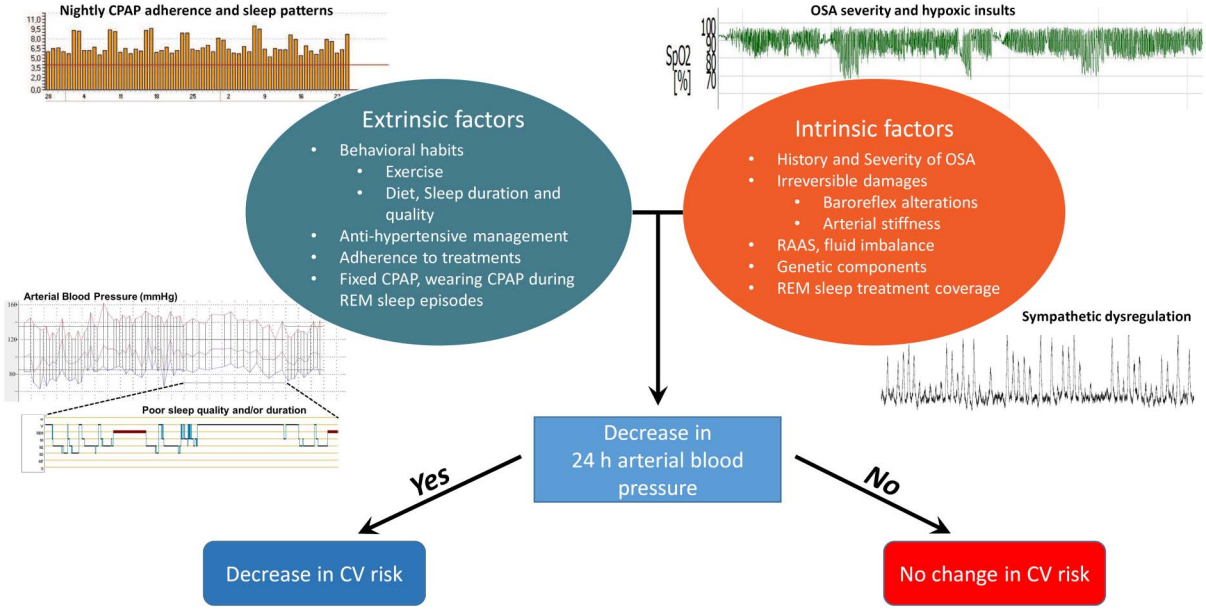

Figure 1 The pathophysiology of OSA-related hypertension. These intrinsic and extrinsic factors may influence the management of hypertension in patients with OSA. OSA severity and duration before diagnosis may have induced irreversible damage to the regulation of blood pressure and the vascular system. RAAS and sympathetic regulation of blood pressure are altered in hypertensive patients with OSA. These pathways could be targeted using antihypertensive drugs as is recommended for diabetics and patients with chronic kidney failure. We need to better identify blood pressure phenotype clusters in order to personalise therapy and ideally to predict response to different treatment strategies.[23] CV, cardiovascular; OSA, obstructive sleep apnoea; RAAS, renin-angiotensin-aldosterone system; REM, rapid eye movement.

influence daytime and night-time blood pressure need to be taken into account in order to design effective strategies for lowering blood pressure in hypertensive patients with OSA (see figure 1). We recently reported that the level of physical activity, as measured by steps per day, was a significant determinant of daytime blood pressure, while the severity of oxygen desaturation during sleep was correlated with morning blood pressure.[18] Accordingly, there is a need for clinical research studies that combine and compare various approaches such as CPAP, medications and physical activity (eg, the RAP clinical trial NCT02057783). Furthermore, interventions that can effectively improve CPAP adherence are essential. A recent report in *Thorax* showed that a better control of 24-hour blood pressure might be obtained by using fixed-pressure CPAP instead of auto-adjusting CPAP,[19] and that wearing CPAP during the majority of REM sleep episodes at the end of the night is central for long-term control of blood pressure.[8] Improving CPAP adherence remains a major goal, as studied in an ongoing trial of auto-adjusting CPAP with a pressure relief technology during periods of night-time wakefulness (NCT02721329).

Surprisingly, although OSA is increasingly recognised as a major chronic disease,[20] with hypertension as a comorbidity in half of patients with OSA, no specific recommendations are available in the international hypertension guidelines except for CPAP therapy. Even in well-defined populations like those with resistant hypertension and OSA, the blood pressure response to CPAP therapy is highly variable and unpredictable. As such, a combination of predictive biomarkers would be particularly helpful to guide clinicians in the management of asymptomatic or minimally symptomatic patients with OSA who are reluctant to accept long-term CPAP therapy.[21 22]

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